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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,062	11/09/2005	Tamas Rujan	82371	8408

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	**PAPER NUMBER**
1637	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,062	RUJAN ET AL.	
	Examiner	Art Unit	
	Suchira Pande	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-51 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-38, drawn to a method for amplification of nucleic acids.

Group II, claim(s) 39-51, drawn to a method for designing primers.

2. The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Laird et al. US Pat. 6, 331,393 B1 issued on December 18, 2001 teaches the method recited in claim 1 (see whole document specially Process D col. 11 lines 56 through col. 15 line 51), namely : a method for the amplification of nucleic acids comprising the following steps

1) isolating a nucleic acid sample,

2) treating said sample in a manner that differentiates between methylated and un-methylated cytosine bases within said sample,

3) amplifying at least one target sequence, within said treated nucleic acid, by means of enzymatic amplification and a set of primer molecules, wherein said primer molecules are characterized in that

a) each primer molecule sequence reaches a predefined measure of complexity,

b) every combination of any two primer molecules in the set has a melting temperature below a specified threshold temperature,

c) every combination of two primer molecules, under conditions allowing for one or more base mismatches per primer, does not lead to the amplification of an unwanted product when virtually tested using the treated and the untreated sample nucleic acids as template, and

4) detecting said amplified target nucleic acid.

Laird et al. do not mention if virtual testing of the primer molecules used was performed as recited in part c) of step 3) in above method.

Lexa et al. 2001 Bioinformatics vol. 17 no. 2. pp 192-193 teach virtual PCR program that processes user given primers, compares them to the sequences in public data bases and prints out potential PCR products (see whole article specially section Algorithm and implementation page 192 par. 2-3) to ensure no unwanted products are formed. Hence Lexa et al. teaches one of ordinary skill in the art how to perform the part c) of step 3) of instant claim 1. Thus all the steps of the recited method were taught by Prior art to one of ordinary skill in the art at the time of the invention. Therefore the method of amplification of invention I does not share the special technical features as the method for designing a primer of group II invention. Hence unity of invention is lacking.

3. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

a. **Species of nature of primer** (claim 1 is generic)

i. primer molecules do not contain nucleic acid sequences complementary or identical to nucleic acid sequences of the target sequence which prior to treatment of step 2 contained a 5'-CG-3' site (claim 2).

ii. primer molecule comprises of at least one nucleotide within the last three nucleotides from the 3' end of the molecule wherein said nucleotide is complementary to a nucleotide of the target sequence that was converted to a different nucleotide by the treatment performed in step 2) of claim 1 (claim 11).

iii. Primer molecule comprises of at least one nucleotide within the last three nucleotides from the 3' end of the molecule wherein said nucleotide is complementary to a nucleotide of the target sequence that was converted to a different nucleotide by bisulfite treatment (claim 12).

iv. primer molecules is characterized in that the last at least 5 bases at the 3' end of said primer molecule are not complementary to the sequence of any other primer molecule in the set (claim 13).

v. Primer molecules are reaching a specified value of linguistic complexity (claim 5).

vi. Primer molecules are reaching a specified value of Shannon entropy (claim 6).

vii. Primer molecules are comprised of 16 - 50 nucleotides (claim 34).

viii. primer molecules do not form dimers with each other (claim 35).

ix. primer molecules do not form loops or hairpin structures (claim 36).

x. primer molecules are complementary to target (claim 37)

b. **Species of nucleic acid sample** (claim 1 is generic)

xi. nucleic acid sample is comprised of plasmid DNA, BACs, YACs or genomic DNA (claim 8)

xii. nucleic acid sample is comprised of human genomic DNA (claim 9)

c. **Species of numbers of primer pairs in a set** (claim 1 is generic)

xiii. set is comprised of at least one but not more than 32 primer pairs (claim3).

xiv. set is comprised of at least one but not more than 16 primer pairs (claim 4).

d. **Species of number of mismatches allowed** (claim 1 is generic)

xv. number of mismatches allowed for when virtually testing the amplification of unwanted products according to step 3 c) of claim 1 is less than 20% of the number of nucleotides of the primer molecule (claim 14).

xvi. number of mismatches allowed for when virtually testing the amplification of unwanted products according to step 3 c) of claim 1 is less than 10% of the number nucleotides of the primer molecule (claim 16).

xvii. number of mismatches allowed for when virtually testing the amplification of unwanted products according to step 3 c) of claim 1 is less than 5% of the number of nucleotides of the primer molecule (claim 18).

xviii. number of mismatches allowed for when virtually testing the amplification of unwanted products according to step 3 c) of claim 1 is less than seven (claim 20).

xix. number of mismatches allowed for is less than five (claim 21)

xx. number of mismatches allowed for is less than three (claim22).

xxi. number of mismatches allowed for is one (claim 23).

xxii. number of mismatches allowed for when virtually testing the amplification of unwanted products according to step 3 c) of claim 1 is determined by a pre-specified maximum melting temperature (claim 24).

e. **Species of number of nucleotides creating one gap allowed for in primer molecule** (claim 1 is generic)

xxiii. the number of nucleotides creating one gap, when aligning the primer molecule sequence with the template sequence, allowed for, when virtually testing the amplification of unwanted products according to step 3 c) of claim 1 is less than 20% of the number of nucleotides of the primer molecule (claim 15).

xxiv. the number of nucleotides creating one gap, when aligning the primer molecule sequence with the template sequence, allowed for, when virtually testing the amplification of unwanted products according to step 3 c) of claim

1 is less than 10% of the number of nucleotides of the primer molecule (claim 17).

xxv. number of nucleotides creating one gap, when aligning the primer molecule sequence with the template sequence, allowed for, when virtually testing the amplification of unwanted products according to step 3 c) of claim 1 is less than 5% of the number of nucleotides of the primer molecule (claim 19).

f. **Species of nature of nucleic acid amplified by primer molecules** (claim 1 is generic)

xxvi. nucleic acid sequences that prior to treatment of step 2 comprised of more than eight 5'-CG-3' sites (claim 25).

xxvii. nucleic acid sequences that prior to treatment of step 2 comprised of more than six 5'-CG-3' sites (claim 26).

xxviii. nucleic acid sequences that prior to treatment of step 2 comprised of more than four 5'-CG-3' sites (claim 27).

xxix. nucleic acid sequences that prior to treatment of step 2 comprised of more than two 5'-CG-3' sites (claim 28).

xxx. nucleic acids which are comprised of at least 50 bp but not more than 2000 bp (claim 32).

xxxi. nucleic acids which are comprised of at least 80 bp but not more than 1000 bp (claim 33).

xxxii. primer molecules amplify regions of the treated nucleic acids which prior to the treatment performed in step 2) of claim 1 did not contain specified restriction enzyme recognition sites (claim 38).

g. **Species of virtual PCR** (claim 1 is generic)

xxxiii. electronic PCR (claim 29)

xxxiv. electronic PCR, taking as template nucleic acid the coding strand of the treated sample, the non- coding strand of the treated sample and both of the strands of the untreated sample (claim 30).

xxxv. electronic PCR, taking as template nucleic acid the coding strand of the bisulfite converted human genome, the non-coding strand of the bisulfite converted human genome and both of the strands of the untreated human genome (claim 31).

h. **Species of measure of complexity (**claim 39 is generic)

xxxvi. measure of complexity is a measure of linguistic complexity (claim 42).

xxxvii. measure of complexity is a measure of Shannon entropy (claim 43).

i. **Species of step carried out prior to performing step d)** (claim 39 is generic)

xxxviii. excluding from the remaining primer pairs those pairs, which consist of a primer molecule that comprises of at least one CpG site (claim 44).

xxxix. excluding from the remaining primer pairs those pairs, which consist of a primer molecule that does not contain at least one nucleotide within the last three nucleotides from the 3' end of the molecule wherein said nucleotide is

complementary to a nucleotide of the target sequence that was converted to a different nucleotide by the treatment performed in step 2) (claim 45)

xl. excluding from the remaining primer pairs those pairs, which consist of a primer molecule that contains more than 5 bases at its 3' end that are complementary to any other primer molecules' sequence in the set (claim 46).

xli. excluding from the remaining primer pairs those pairs, which amplify a nucleic acid that did not, prior to the treatment in step 2 contain at least two CpG sites (claim 47).

xlii. excluding from the remaining primer pairs those pairs, which comprise of one primer molecule that in combination with another primer molecule in the set amplifies an unwanted product, when virtually testing according to step 3 c) under conditions allowing for a number of mismatching nucleotides of 20% of the number of nucleotides of the primer molecule (claim 48).

xliii. excluding from the remaining primer pairs those pairs, which comprise of one primer molecule that in combination with another primer molecule in the set amplifies an unwanted product, when virtually testing according to step 3 c) under conditions allowing for a number of nucleotides creating one gap, when aligning the primer molecule sequence with the template sequence, of up to 20% of the number of nucleotides of the primer molecule (claim 49).

xliv. excluding from the remaining primer pairs those pairs, which comprise of one primer molecule that in combination with another primer molecule in the set amplifies an unwanted product, when virtually testing according to step 3 c) under conditions allowing for four or less mismatching base pairs (claim 50).

xlv. excluding from the remaining primer pairs those pairs, which comprise of one primer molecule that in combination with another primer molecule in the set amplifies an unwanted product, when virtually testing according to step 3 c) under conditions allowing for two or less mismatching base pairs (claim 51).

4. Applicant is required, in reply to this action, to elect a **single species** from each of the categories **a) through i)** enumerated above to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

5. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

a) Species of nature of primer claimed has different limitations associated with each primer molecule enumerated.

b) Species of nucleic acid sample: each of the nucleic acid claimed is recognized in the art as distinct and different.

c) Species of numbers of primer pairs in a set: the numbers of primer pairs comprising the set are different.

d) Species of number of mismatches allowed that are claimed are different resulting in different constraints on the primers claimed.

e) Species of number of nucleotides creating one gap allowed for in primer molecule : the percentages of gap allowed that are claimed are different.

f) Species of nature of nucleic acid amplified by primer molecules claimed are different thus requiring different searches.

g) Species of virtual PCR claimed requires different constraints while performing the electronic PCR.

h) Species of measure of complexity: the methods claimed are two different methods based on different algorithms.

i) Species of step carried out prior to performing step d) the steps recited are different hence require different searches.

6. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Teresa Strzelecka/

Teresa Strzelecka
Primary Examiner, Art Unit 1637

December 11, 2007